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PATENT
Attorney Docket No. 205654

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Kovesdi et al.

Art Unit: 1647

Application No. 09/832,355

Examiner: Spector, L.

Filed: April 10, 2001

For: VEGF FUSION PROTEINS

**PENDING CLAIMS AFTER AMENDMENTS
MADE IN RESPONSE TO OFFICE ACTION DATED OCTOBER 23, 2002**

1. A fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis or bone growth, and wherein the second peptide portion lacks a collagen binding domain.
2. The fusion protein of claim 1, wherein the first peptide portion comprises a VEGF-A peptide portion which exhibits a higher affinity for KDR receptors than flt receptors or flk receptors.
3. The fusion protein of claim 2, wherein the VEGF-A peptide portion exhibits about equal or less affinity for neuropilin-1, neuropilin-2, or both, as VEGF₁₂₁.
4. The fusion protein of claim 3, wherein the first peptide portion comprises a wild-type VEGF-A amino acid sequence of about 150 amino acid residues or less.
5. The fusion protein of claim 1, wherein the first peptide portion comprises VEGF₁₂₁.
6. The fusion protein of claim 1, wherein the fusion protein has a half-life in a mammalian host at least twice as long as the half-life of a protein consisting essentially of either the first peptide portion and/or at least twice as long as the half-life of a protein consisting essentially of the second peptide portion.

7. The fusion protein of claim 6, wherein the fusion protein has a half-life of at least about 10 minutes in a mammalian host.

8. The fusion protein of claim 7, wherein the second peptide portion comprises a peptide lacking its native multimerization domain or a peptide comprising a non-functional multimerization domain.

9. The fusion protein of claim 1, wherein the fusion protein is more angiogenic than a protein consisting essentially of the first peptide portion and/or is more angiogenic than a protein consisting essentially of the second peptide portion.

12. The fusion protein of claim 9, wherein blood vessels resulting from administration of the fusion protein to a mammalian host are associated with more smooth muscle cells, a greater concentration of smooth muscle cells, more endothelial cells, a greater concentration of endothelial cells, or any combination thereof, than blood vessels resulting from administration of a protein consisting essentially of the first peptide portion.

13. The fusion protein of claim 1, wherein the second peptide portion comprises a receptor ligand which is present on a native endothelial cell.

16. The fusion protein of claim 1, wherein administration of the fusion protein to an area in a mammalian host results in greater blood flow in the area of administration than the administration of a protein consisting essentially of the second peptide portion.

17. The fusion protein of claim 1, wherein the second peptide portion comprises a peptide which promotes blood vessel wall maturation, blood vessel wall dilatation, blood vessel remodeling, extracellular matrix degradation, decreases blood vessel permeability, or any combination thereof.

18. The fusion protein of claim 1, wherein the fusion protein is free of any immunoglobulin domains.

19. The fusion protein of claim 1, wherein the second peptide portion comprises an angiopoietin, a fibroblast growth factor, a member of the HBNF-MK family of growth

factors, an alkaline phosphatase, or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof.

20. The fusion protein of claim 19, wherein the second peptide portion comprises a peptide that is about 25% or more homologous to angiopoietin-1.

21. The fusion protein of claim 20, wherein the second peptide portion comprises a domain which exhibits about 35% or more homology to the fibrinogen-like domain of Ang-1.

22. The fusion protein of claim 21, wherein the second peptide portion comprises angiopoietin-1 or an angiogenically functional fragment thereof.

23. The fusion protein of claim 22, wherein the second peptide portion comprises an N-terminal truncated form of angiopoietin-1, and the truncated form comprises about 60% or less of the wild-type angiopoietin-1 amino acid sequence.

24. The fusion protein of claim 23, wherein the second peptide portion lacks the multimerization domain of angiopoietin-1.

25. The fusion protein of claim 24, wherein the fusion protein is free of any immunoglobulin domains.

26. The fusion protein of claim 21, wherein the second peptide portion comprises the peptide encoded by KIAA0003.

27. The fusion protein of claim 19, wherein the second peptide portion comprises an acidic fibroblast growth factor or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof.

28. The fusion protein of claim 19, wherein the second peptide portion comprises a member of the HBNF-MK family of growth factors or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof.

30. The fusion protein of claim 28, wherein the second peptide portion comprises HBNF or MK, or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or a combination thereof.

31. The fusion protein of claim 30, wherein the second peptide portion comprises an N-terminal truncated form of HBNF or MK including at least about 60% of the wild-type HBNF or MK amino acid sequence.

32. The fusion protein of claim 1, wherein:

- (a) the amino acid sequence of the first peptide portion or second peptide portion, within about 15 amino acids of the fusion point of the fusion protein, lacks an amino acid residue corresponding to an amino acid residue in its wild-type counterpart, or
- (b) the fusion protein further comprises a linker positioned between the first peptide portion and second peptide portion.

33. A polynucleotide comprising a nucleotide sequence which, when expressed in a cell permissive for expression of the nucleotide sequence, results in the production of a fusion protein according to claim 1.

34. A vector comprising the polynucleotide of claim 33.

35. The vector of claim 34, wherein the vector is a replication deficient adenoviral vector.

36. The vector of claim 35, wherein the replication deficient adenoviral vector comprises or expresses a modified adenoviral protein, non-adenoviral protein, or both, which increases the efficiency that the vector infects cells as compared to wild-type adenovirus, allows the vector to infect cells which are not normally infected by wild-type adenovirus, results in a reduced host immune response in a mammalian host as compared to wild-type adenovirus, or any combination thereof.

37. The vector of claim 36, wherein the polynucleotide comprises a nucleotide sequence which upon expression results in a fusion protein comprising VEGF121 fused to (a) angiopoietin-1, (b) an acidic fibroblast growth factor, (c) a HBNF, (d) a MK, (e) an alkaline phosphatase, or (f) a fragment of any of (a)-(e) which promotes angiogenesis, bone growth, or wound healing.

38. The vector of claim 37, wherein the polynucleotide comprises a second nucleotide sequence that, when expressed, produces a second protein which promotes angiogenesis, bone growth, wound healing, or any combination thereof, and wherein the nucleotide sequence which results in the production of the fusion protein is operably linked to a first promoter and the second nucleotide sequence is operably linked to a second promoter, such that the initiation of expression of the first nucleotide sequence and the second nucleotide sequence occurs at different times, in response to different factors, or both.

39. A method of promoting angiogenesis, bone growth, wound healing, or any combination thereof in an individual comprising administering to the individual an amount of the fusion protein of claim 1 effective to promote angiogenesis, bone growth, wound healing, or any combination thereof.

40. A method of producing a fusion protein comprising introducing the vector of claim 34 into a cell such that the nucleotide sequence is expressed to produce a fusion protein.

41. A method of producing a fusion protein comprising introducing the vector of claim 35 into a cell such that the polynucleotide is expressed to produce a fusion protein.

43. A fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis, bone growth, wound healing, or any combination thereof, wherein the VEGF peptide portion is at least about 115 amino acids in length and the second peptide portion lacks a collagen binding domain.

44. The fusion protein of claim 43, wherein the second peptide portion promotes angiogenesis.

45. The fusion protein of claim 44, wherein the second peptide portion promotes angiogenesis or bone growth more than wound healing.

46. The fusion protein of claim 45, wherein the fusion protein does not comprise a functional collagen binding domain.